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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Sandra M. Sims) DOCKET NO.: 3523/2/US
SERIAL NO.: 09/933,366) GROUP ART UNIT: 1614
FILED: August 20, 2001) EXAMINER: Cybille Celacroix
TITLE: SOLUTION COMPOSITION OF A OXAZOLIDINONE ANTIBIOTIC
DRUG HAVING ENHANCED DRUG LOADING

CERTIFICATE OF MAILING

I hereby certify that this document and accompanying documents referred to herein are being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, U.S. Patent and Trademark Office, Box Response, Washington, DC 20231 on August 29, 2002.

Mary Katriadakis
Mary Katriadakis

Assistant Commissioner for Patents
U.S. Patent and Trademark Office
Box Response
Washington, DC 20231

DECLARATION BY MICHAEL R. BARBACHYN, UNDER 37 CFR 1.132

Sir:

I, Dr. Michael R. Barbachyn, declare that:

1. I am an employee of Pharmacia Corporation, the assignee of the above-cited invention. I make this declaration in an attempt to further the prosecution of the application.
 2. I received a B.S. degree in Chemistry from Calvin College, Grand Rapids, Michigan in 1979, and a Ph.D. in Organic Chemistry at Wayne State University, Detroit, Michigan in 1983. I was a National Institutes of Health postdoctoral fellow at Yale University, New Haven, Connecticut from 1983 to 1985.

3. I have many years of experience synthesizing and formulating biologically active compounds, especially novel antibacterial, antifungal, and antiviral agents, beginning at least as early as 1980. I began my career as a research scientist at Upjohn Company in 1985. Upjohn eventually became Pharmacia & Upjohn Company, which eventually became Pharmacia Corporation (hereinafter, collectively referred to as "Pharmacia"). In 1996, I became the Program Team Leader for the Oxazolidinone Antibacterials group at Pharmacia. I then left Pharmacia to work as the Group Leader of the Hepatitis C (HCV) RdRp Inhibitors group at Bristol-Myers Squibb Company from 1998 to 1999. In 1999, I returned to Pharmacia, where I worked as a Senior Scientist V in research and development, until 2000, when I became the Associate Director of Combinatorial and Medicinal Chemistry Research, a position I currently hold.
4. I am the author or co-author of at least thirty-two publications and have given numerous public presentations at various scientific meetings, many of which publications and presentations dealt with the synthesis and properties of oxazolidinones and other antibacterial agents. I am also the inventor or co-inventor of at least thirty United States Patents. A copy of my *curriculum vitae* is attached as Exhibit A.
5. I have reviewed an Office Action from the U.S. Patent and Trademark Office, mailed March 29, 2002, and the two references cited therein, U.S. Patent Number 5,699,792 for an invention by Barbachyn *et al.* (hereinafter, "Barbachyn *et al.*") and U.S. Patent Number 5,646,294 for an invention by Bartroli *et al.* (hereinafter, "Bartroli *et al.*"). I am a co-inventor of the subject matter of the first of the two references cited in the Office Action, the Barbachyn *et al.* patent. I understand that all the claims of the present application were rejected as being unpatentable over Barbachyn *et al.* in view of Bartroli *et al.*. For reasons given below, I believe that the present invention would not have been obvious over the two cited references at the time the present application was filed.

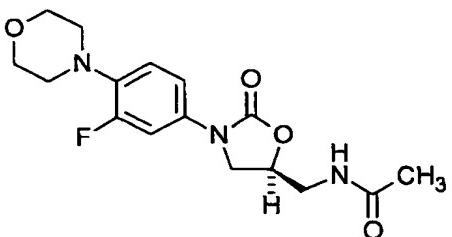
6. Barbachyn *et al.* is cited in the Office Action as disclosing oxazolidinone compounds combined with various solid or liquid pharmaceutically acceptable carriers to make various formulations, including injectable formulations. (Office Action, p. 3). The Office Action goes on to note that the same reference does "not disclose adding a cyclodextrin to the composition." (*Id.*). Bartroli *et al.* is cited as disclosing orally active antifungals "formulated into injectable compositions containing an aqueous carrier and cyclodextrins, e.g. Hydroxypropyl-beta-cyclodextrin, as solubilizing agents." (Office Action, p. 4, citing Bartroli *et al.*, col. 14, lines 43-48). The Office Action then states that:

"It would have been obvious to one of ordinary skill in the art to modify the methods and composition of Barbachyn *et al.* to include the cyclodextrins taught by Bartroli *et al.* because Bartroli *et al* disclose that the cyclodextrins enhance the solubility of the antifungal agents." (Office Action, p. 4)

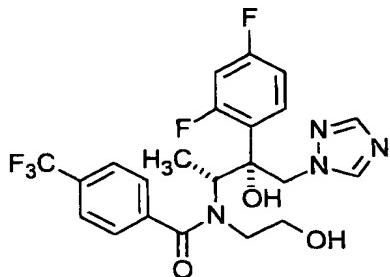
I disagree with this last statement, for the following reasons.

7. Cyclodextrins are donut-shaped molecules, each with a hydrophobic cavity that can incorporate a variety of guest molecules of suitable size and shape, resulting in increased solubility of many different poorly soluble, lipophilic drugs in the presence of cyclodextrins. Several factors have been found to be responsible for the solubility of such drugs in cyclodextrins. Of those factors, hydrophobic interaction is often cited as the most important factor responsible for the incorporation of guest molecules into the hydrophobic interior of a cyclodextrin cavity. The azole antifungal agents described as being solubilized by cyclodextrins in Bartroli *et al.* are examples of the very type of poorly soluble lipophilic drugs of a suitable size and shape to fit into the hydrophobic interior of a cyclodextrin cavity that one would expect to be solubilized by cyclodextrins.
8. Oxazolidinones, on the other hand, such as those described in Barbachyn *et al.* are of a completely different size and structure than the azole antifungal agents disclosed in Bartroli *et al.* Example 5 of Barbachyn *et al.* describes a process for making a representative oxazolidinone compound of Formula I of that application, hereafter referred to as linezolid (marketed as ZyvoxTM by Pharmacia Corporation).

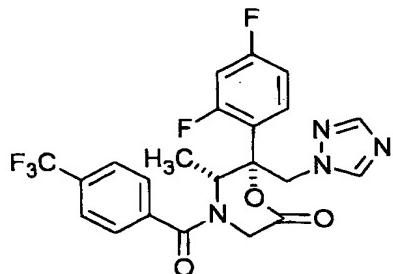
One can clearly see differences between the azole antifungal agents of Bartroli *et al.* and the oxazolidinones of Barbachyn *et al.* by comparing the structure and properties of the representative oxazolidinone, linezolid, to two azole antifungal agents disclosed in Examples 3 and 53, of Bartroli *et al.*, representative examples of compounds of Formulas I and I' of that reference, respectively. The chemical structures of all three compounds are provided herein, below.



US Patent 5,688,792
Formula I (Example 5,
generic name linezolid,
marketed as Zyvox™)



US Patent 5,646,294
Formula I (Example 3)



US Patent 5,646,294
Formula I' (Example 53)

9. Linezolid has a molecular weight of 337.35. In contrast, the azole antifungal agents of Examples 3 and 53 have molecular weights of 484.42 and 480.39, respectively. Cyclodextrins have a defined space available for incorporating or clathrating their substrates. Given the substantial differences in molecular weight and attendant steric size/shape between linezolid and Examples 3 and 53, it is not obvious that cyclodextrins would enhance the solubility of linezolid.
10. Linezolid is also considerably less lipophilic than the two representative antifungal agents disclosed by Bartroli *et al.*, cited above. The apparent lipophilicity of linezolid was determined by measuring the partition coefficient (PC) between *n*-

octanol and water. The experimentally determined log PC value of 0.55 strongly suggests that this drug is an amphophilic compound. That is, it possesses both hydrophobic and hydrophilic characteristics. We found that a software program predicted a log PC value of 0.76 for linezolid, remarkably close to the experimental value. Employing this same program to calculate the log PC's for the azole antifungal agents disclosed in Example 3 and 53 affords values of 2.32 and 3.19, respectively. In other words, the azole antifungals exemplified by Examples 3 and 53 are dramatically more lipophilic/hydrophobic than the oxazolidinone antibacterial agent, linezolid. This fact, combined with the known affinity of cyclodextrins for highly hydrophobic molecules suggests that, although the increased solubility of the azole antifungal agents disclosed by Bartroli *et al.* in the presence of cyclodextrins would be expected, the same would not hold true for linezolid and other oxazolidinones. (C)

11. Linezolid also has a considerably lower pK_a from compared to the two azole antifungal agents discussed above. Linezolid is a weakly basic compound, with $pK_a = 1.8$. In contrast, itraconazole, a marketed antifungal agent incorporating a 1,2,4-triazole ring system and, therefore, related to Examples 3 and 53 of Bartroli *et al.*, has a $pK_a = 3.70$. In other words, itraconazole and, by association, the azole antifungal agents of Examples 3 and 53, is considerably more basic than linezolid. One would expect this difference in basicity to influence the interaction between the compounds and cyclodextrins. Therefore, it is not obvious that linezolid could be solubilized by cyclodextrins, merely because considerably more basic compounds such as the azole antifungal agents of Examples 3 and 53 of Bartroli *et al.* can be.
12. Linezolid also differs significantly from azole antifungals in its functionality. Specifically, linezolid and other oxazolidinones are not substrates for cytochrome P-450 enzymes. In contrast, members of the azole antifungal class, presumably also including Examples 3 and 53, since they incorporate the 1,2,4-triazole ring associated with this inhibition, reversibly inhibit cytochrome P-450 3A. This sort of interaction leads to drug-drug interactions. It is interesting to note that linezolid's structural and electronic properties are such that it is not a substrate for this enzyme. Due to this difference in basicity, one would expect linezolid to interact with

cyclodextrins in a completely different manner from the azole antifungal compounds disclosed by Bartroli *et al.*, including those of Examples 3 and 53. One would not expect linezolid to be solubilized by cyclodextrins merely because Bartroli *et al.* indicates that at least some azole antifungal compounds are solubilized by cyclodextrins.

13. Although only three specific compounds are specifically discussed above, one disclosed by Barbachyn *et al.* and the other two disclosed by Bartroli *et al.*, I would expect the same general principals apply to the complete class of compounds disclosed by each reference. For all of the reasons set forth herein above, therefore, I submit that it would not have been obvious to use the cyclodextrin compounds shown by Bartroli *et al.* to be useful in solubilizing specific azole antifungal compounds, such as those of Examples 3 and 53, to make the oxazolidinone formulations of the present invention. Specifically, the size, molecular weight, hydrophobicity, and basicity of the azole antifungal compounds are too different from those same properties of the oxazolidinones, including linezolid, for one to expect the oxazolidinones to be solubilized in the presence of cyclodextrins merely because the same can be said of the azole antifungal compounds.
14. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and such willful false statements may jeopardize the validity of an application or any patent issuing thereon.

Michael R. Barbachyn

Michael R. Barbachyn

8/28/02

Date



EXHIBIT A

CURRICULUM VITAE

Name: Michael R. Barbachyn
Unit Name: Combinatorial and Medicinal Chemistry Research
Pharmacia Corporation
Kalamazoo, MI 49001
Title: Associate Director

EDUCATION

1983-1985 NIH Postdoctoral Fellow, Yale University, New Haven, CT (Professor Samuel J. Danishefsky, advisor)
1983 Ph.D., Organic Chemistry, Wayne State University, Detroit, MI.
Thesis: β -Hydroxysulfoximine-Directed Cyclopropanations and Osmylations (Professor Carl R. Johnson, advisor)
1979 B.S., Chemistry, Calvin College, Grand Rapids, MI

EMPLOYMENT HISTORY

2000-present Pharmacia Corporation
Associate Director
1999-2000 Pharmacia & Upjohn
Senior Scientist V
1998-1999 Bristol-Myers Squibb Company
Group Leader – Hepatitis C (HCV) RdRp inhibitors
1985-1998 Pharmacia & Upjohn and The Upjohn Company
1996-1998 Program Team Leader - Oxazolidinone Antibacterials
1996-1998 Senior Scientist IV
1992-1996 Senior Research Scientist III
1988-1992 Research Scientist II
1985-1988 Scientist I

HONORS

Upjohn Award (2001)
Fred Kagan Lead Finding Award (1995)

Fred Kagan Lead Finding Award (1987)
NIH Postdoctoral Fellowship (1983-1985)
Graduate Fellow at Wayne State University (1981-1983)
Recipient of NSF Undergraduate Research Participant Grant (1978)
Roger B. Chaffee Memorial Scholarship Recipient (1974-1975)

PROFESSIONAL MEMBERSHIPS

American Chemical Society

CURRENT AREAS OF SCIENTIFIC INTEREST

Synthesis of biologically active compounds, especially novel antibacterial, antifungal and antiviral agents. Synthetic methodology, especially asymmetric transformations and transition metal mediated processes.

PATENTS

Inventor or co-inventor of at least 30 U.S. patents. Additional patent applications pending.

PUBLICATIONS

Author or co-author of at least 32 scientific articles.